Amendments to the Drawings:

Please enter the enclosed amended figures 1 and 2, which, in accordance with 37 CFR 1.121(d), are attached hereto, and are labeled "Replacement Sheet" in the top margin.

Attachment: Replacement Sheets
Annotated Sheets Showing Changes

The changes are also explained in the remarks.

REMARKS

1. Applicant elects group I (claims 1, 3-7, 9, 11, 13, 15, 17-18, 20-30) with traverse.

The group-level restriction (I-IV) is traversed on the following grounds.

The restriction requirement is based on alleged lack of novelty over Matsushita et al., 2002 cited in the IDS filed October 13, 2005. Applicant respectfully disagrees and requests that novelty of all claims is acknowledged for the following reasons.

In the IDS of October 13, 2005 two documents by Matsushita et al., 2002 were cited namely, Matsushita et al., 2002, J. Immunol., 168:3502-3506 (herein after referred to as Matshushita et al., 2002) and Matsushita and Fujita, 2002, Immunobiol., 205:490-497 (herein after referred to as Matshushita and Fujita, 2002). The following discussion thus relates to both documents.

The present invention relates to fusion proteins comprising a sequence derived from a lectin-complement pathway activating protein, for example a ficolin and a sequence derived from a collectin, for example MBL. The term "fusion protein" is well established in the art and refers to a protein created through genetic engineering from two or more proteins/peptides (see for example Methods in Enzymology (1990) Vol. 185:129 [12] Gene Fusions for Purpose of Expression: An introduction. Uhlén, M. and Moks, T.).

Matsushita et al., 2002 describes isolation of H-ficolin, L-ficolin and MBL from human plasma. The document furthermore describes that ficolins and MBL in plasma may be associated with MBL-associated serine proteases (MASPs). Nowhere does the document describe fusion proteins. In fact, the document nowhere describes any protein prepared using genetic engineering.

Matsushita and Fujita, 2002 describes the innate immune system. The document inter alia describes activation of the

lectin pathway by ficolins. The document furthermore describes that ficolins and MBL in plasma may be associated with MBL-associated serine proteases (MASPs). Nowhere does the document describe any fusion proteins.

Furthermore, as is apparent from the document MASPs are not lectin-complement pathway activating proteins, but rather the lectin-complement pathway is activated by activation of MASPs, for example by ficolins (see for example p. 493, 6th paragraph). It is described by the present invention, that lectin-complement pathway activating proteins preferably are capable of associating with MASP, thereby being capable of complement system activating activity (see description p. 18, 39 to p. 19, l. 2). It is thus apparent that the term "lectin-complement pathway activating protein" does not include MASP.

Accordingly, applicant respectfully submits that the fusion proteins according to claim 1 indeed are novel over both publications by Matsushita, 2002. Accordingly, nucleic acids encoding such proteins, vectors comprising such nucleic acids, cells comprising such vectors as well as methods and compositions employing or comprising said fusion proteins are also novel.

2. The first full paragraph page 4 of the restriction nominally requires Applicants to elect a single SEQ ID NO:. However, in a telephonic interview held December 27, Examiner Mondesi advised Counsel that it would be sufficient to elect one sequence for the "first polypeptide" and one for the "second polypeptide". As "first polypeptide", we elect with traverse human L-Ficolin which is amino acids 1-77 of SEQ ID NO:125, see Fig. 1 and P12, L7-19. As "second polypeptide", we elect with traverse human MBL which is amino acids 80-228 of SEQ ID NO:126, see Fig. 2. Note that Fig. 3 depicts a fusion of human L-Ficolin to human MBL. Hence, if we still need to elect a single fusion protein, we elect the protein of Fig. 3, and in particular SEQ ID NO:129, depicted in Fig. 3.

We traverse this restriction on several grounds.

2.1. The Examiner is clearly aware that this case is the national stage of a PCT application, hence, PCT unity rules apply. While the Examiner may, under authority of 35 USC 121, reexamine the issue of unity of invention, 35 USC 372 (b)(3) requires that it be conducted "within the scope of the requirements of the treaty and the Regulations".

In that regard, we respectfully direct the Examiner's attention to the PCT Administrative Instructions Annex B, paragraph (c).

This states the general principle that "unity of invention has to be considered in the first place only in relation to the independent claims in an international application and note the dependent claims".[1] The only claims which are "independent" in the PCT sense are claims 1 (fusion protein), 31 (nucleic acid)[2] and 37 (method, thus a different category of claim).

In contrast, the claims identifying the first polypeptide (3-7, 9, 11, 13, 15) or the second polypeptide (17, 18, 20-26) are dependent claims (all dependent on 1).

Clause (i) states that "if the independent claims avoid the prior art..., no problem of lack of unity arises in respect of any claims that depend on the independent claims".

It elaborates upon this as follows:

1) "it does not matter if a dependent claim itself contains a further invention"

2) "no problem arises in the case of a genus/species situation where the genus

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[1] The definition of a "dependent claim" under international practice is "a claim which contains all the features of another claim and is in the same category as that other claim". As examples of "categories", the definition gives "product", "process", "use" and "apparatus".

[2] Arguably 31 is a product claim, like 1, but since the nucleic acid doesn't include amino acids we are not sure it can be characterized as including all features of 1 and hence we treat it as independent for PCT purposes.

> claim avoids the prior art".
>
> 3) "no problem arises in the case of a combination/subcombination situation where the subcombination avoids the prior art and the combination claim includes all the features of the subcombination".

The next subparagraph (ii) informs the Examiner of what to do if "an independent claim does not avoid the prior art". In essence, the Examiner must consider "whether there is still an inventive link between all the claims dependent on that claim". If not, then, and only then, the Examiner may find a "lack of unity a posteriori (that is, arising only after assessment of prior art).

This (c)(ii) procedure is clearly applicable to the genus/species situation, as is made explicit by the last sentence of (c)(i).

The Examiner has made an assessment of prior art against claim 1, and made an initial determination that claim 1 is not patentable over Matsushita. If that determination is correct (we challenge it in section 1 above), then the next step would be for the examiner to determine whether there are any "links".

The Examiner says in the paragraph bridging pp. 3-4:

> Furthermore, the presence of multiple polypeptide sequences and polynucleotide sequences, each with a different SEQ ID NO: allows for a variety of patentably distinct products. Depending on the sequences of each polypeptide and polynucleotide, the characteristics of the resulting molecule will vary in regards to structure and function. Each one of these polypeptides is capable of eliciting a specific immune response and can be used to produce a specific antibody; also each one of the mentioned polynucleotides is capable of hybridizing to different probes and is capable of encoding a characteristically different peptide in regards to structure and activity. Therefore these polypeptides and polynucleotides are patentably distinct

> absent factual evidence to the contrary. Rejoinder of all or a specified subset of the sequences is possible if Applicants provide a single and specific representative subsequence found in all or a specified subset of the sequences for search, and state that all or a specified subset of the sequences are not patentably distinct. Applicants are informed that if their specified sequence is found that all or a specified subset of sequences are obvious over that prior art sequence.

We appreciate that the purpose of this statement is to invite Applicants to establish that linking subject matter exists. However, paragraph (c)(ii) clearly imposes upon the Examiner the burden of establishing at least a prima facie case that the links don't exist. In this respect, international practice is different from domestic practice.

2.2. We also don't understand why the restriction is characterized as a "response to a restriction requirement of a patentably distinct product, not an election of species".

The Examiner has already recognized that this is a national stage of a PCT, and international unity rules apply. We are not aware of any separate election of species practice under PCT regulations.

In domestic practice, for a species restriction to be proper, the species must be patentably distinct from each other. See MPEP 806.04(h). Hence, patentable distinctness by itself is not a proper basis for treating the sequence as something other than a species. Legally, all domestic restriction practice is based on 37 CFR 1.141. While 37 CFR 1.146 specifically addresses "election of species", it is as a subset of 1.141 practice, which itself refers to species practice.

The "election of species" practice is a subset of the more general practice dealing with "linking" claims.

In some instances, the propriety of a restriction is dependent on whether or not one or more linking claims are

allowable.

Under domestic restriction practice, the examiner can restrict initially, and rejoin if the linking claims are found allowable.

Under PCT unity practice, that the examiner must make a prima facie showing that the claims don't have a common special technical feature before restricting (EPO calls this a posteriori lack of unity).

Indeed, the restriction among groups I-IV was based on a holding (challenged in section 1 above) that the fusion protein per se (which is in fact claimed directly) is anticipated, therefore justifying restriction of the protein, from the nucleic acid, pharmaceutical composition, method of use, etc.

If a claim is a "linking claim" in the domestic sense, it comprises one or more special technical features in the PCT sense.

If a linking claim is held allowable, linked claims are rejoined. Under domestic practice, linking claims include

(A) genus claims linking species claims;

(B) subcombination claims linking plural combinations; and

(C) product claims linking dependent methods of making and use.

See MPEP 809, 809.03, 814 (III), and 821.04.

It appears that, by designating the sequence restriction as an ordinary restriction and not an election of species, the examiner is implying that there is no genus claim. However, that plainly is inaccurate, see e.g., claim 1.

2.3. In any event, in response to the paragraph bridging pp. 3-4, we have prepared an alignment of the suggested first polypeptides mentioned on pages 11 to 18 in the application as filed (enclosed as Exhibit A). It is apparent from the alignment that the different first polypeptides share a high

degree of homology. Most notably, they share the repetitive motif X-X-G-X-X-G, which is described in the application p. 19, l. 20-22. Furthermore, several other residues are conserved.

With regard to the second polypeptides, we have prepared several different alignments. When comparing all the second polypeptides described on pages 20 to 81 at sequence level no specific motif shared by all of the second polypeptides is apparent. However, when preparing an alignment of all sequences identified as Mannose Binding Lectins, precursors of Mannose Binding Lectins or Mannose Binding Lectin-like (SEQ ID NO 2, 3, 8, 9, 15, 16, 18, 19, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 32, 33, 34, 35, 36, 37, 38 and 40) it is apparent that they are very similar (see enclosed Exhibit B). These proteins also comprise the X-X-G-X-X-G motif, however preferably the second polypeptides comprise a CRD domain (see p. 19, l-. 30-31), which is found in the C-terminus of MBL (see figure 9). Shared motifs in the C-terminal part of the second polypeptides include a W-X-D-X-X-C motif (aa 227-232 of SEQ ID NO: 2) and a Y/F- S/T- N-W-X-X-X-E/Q-P-D/N-D/N motif (aa 201-211 of SEQ ID NO: 2).

It is thus apparent that the first polypeptides such as L-ficolin share similarities in structure and function, and also that at least some of the second polypeptides such as MBL also share similarities in both structure and function.

2.4. We also respectfully direct the Examiner's attention to MPEP §2434. This partially waived the requirements fo 37 CFR 1.141 to allow "in most cases, up to 10 independent and distinct nucleotide sequences... in a single application without restriction". We see no reason that this waiver should apply only to nucleotide sequences and not to amino acid sequences, both being searched at the USPTO using the same software suite.

Moreover, according to MPEP 2434, "those sequences which are patentably indistinct from the sequences selected by

applicant will also be examined".

MPEP §2434 evidences that it is not unduly burdensome to search up to independent sequences, whether they be nucleotide or amino acid sequences". Under MPEP 808.02, restriction is proper only where there is a "serious burden" on the examiner if restriction is not required. We believe that 808.02 properly applies even to international cases, because the PCT only requires that national practice not be more restriction than PCT practice; it is permitted to be more liberal.

3. In a telephonic interview conducted on January 18, Examiner Mondesi confirmed that there is a typographical error in the restriction, pages 4 and 5: the reference to claim 6 should be to claim 4, and the one to claim 8 should be to claim 6.

Examiner Mondesi also clarified in that interview that applicants should make separate species elections for each of claims 4, 6, 17, and 21-24. In this regard it is noted by Counsel that claim 4 relates to which MASP protein the "first polypeptide" associates with; claim 6 to the identity of the first polypeptide/complement activating protein, and claims 17 and 21-24 to the identify of the second polypeptide/collectin.

Applicants hereby elect, all with traverse, as follows:

For claim 4, MASP-2

For claim 6, L-ficolin

For claim 17, MBL

For claims 21-24, the CRD domain of MBL.

4. Several claims have been amended to avoid recitation of "functional homologue". The recitations of 70% identity and activity were retained, and claim 1 now explicitly recites fragments per P18, L32-37 and P81, L45-50. See also P85, L3-P91, L2. We have also added some new claims based on e.g., P18, L32 to P19, L25 and P81, L45-P83, L6.

The preferred fusion proteins of the invention in general only comprise a fragment of the Lectin-complement pathway

activating protein and a fragment of the collectin. The most preferred fusion proteins comprise the N-terminus of L-ficolin and the C-terminus of MBL. Examples of such fusion proteins are given in Example 1 (SEQ ID NO:118-124), figure 3 (SEQ ID NO:127) and figure 9 (SEQ ID NO:118-122), wherein SEQ ID NO:127 represents the currently most preferred fusion protein. SEQ ID NO:127 comprises a fragment of L-Ficolin (aa 1-77 of SEQ ID NO:125) and a fragment of MBL (aa 80-228 of SEQ ID 126).

Thus, the claimed first polypeptide sequence comprises at least 30 consecutive amino acids of SEQ ID NO:125, or a 70%+ mutant thereof and the currently most preferred first polypeptide sequence is aa 1-77 of SEQ ID NO:125. The claimed second polypeptide sequence comprises at least 30 consecutive amino acids of SEQ ID NO:126, or a 70%+ mutant thereof and the currently most preferred second polypeptide sequence is aa 80-228 of SEQ ID NO:126.

It is perhaps worth noting that the most preferred first polypeptide, Aas 1-77 of SEQ ID NO:125, is a fragment which is 27% of mature L-ficolin (284 a.a.), whereas the most preferred second polypeptide, Aas 80-228 of SEQ ID NO:126, is 65% of mature MBL (228 a.a.).

Other explicitly disclosed fragments include: 1-50, 1-54, 1-55, 1-69, 1-90, 1-93, 1-131, 1-207, 60-90, 55-90 and 54-92 of L-ficolin (P19, L4-18), and 170-200, 160-200, 150-200, 140-200, 130-200, 120-200, 110-200, 90-200, 80-200, 70-200, 60-200, 56-228, 55-228, 54-228 and 50-228 of MBL (P82, L9-P83, L3).

It is clearly contemplated that the first polypeptide can be a fragment of a variant/homologue of a complement activation protein (or equivalently, a variant/homologue of a fragment), see P18, L32-37. Likewise, the second polypeptide can be a fragment of a variant/homologue of a collectin (or equivalently, a variant/homologue of a fragment), see P81, L45-50.

5. Figures 1 and 2 are amended herewith. The sequence depicted in Figure 1 is 284 a.a. long, and corresponds to mature human L.ficolin, SEQ ID NO:125. However, the text of Figure 1 erroneously states that the sequence is 313 a.a. long and corresponds to the L-ficolin precursor. The 313 a.a. sequence of L.ficolin precursor is shown in Fig. 9 (SEQ ID NO:139). We have amended Figure 1 by removing the problematic text.

Likewise, the sequence depicted in Figure 2 is 228 a.a. long, and corresponds to mature human mannose binding lectin SEQ ID NO:126. However, the text of Figure 2 erroneously states that the sequence is 248 a.a. long and corresponds to the ML precursor. The 248 a.a. sequence of MBL precursor is shown in Figure 9 (SEQ ID NO:9). Additionally, the text "248 a.a." partially overwrites the second line of the sequence.

We have amended Figure 2 by removing the problematic text.

Respectfully submitted,

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Enclosures
-Exhibit A
-Exhibit B
-Replacement Figures 1 and 2
-Annotated Figures 1 and 2

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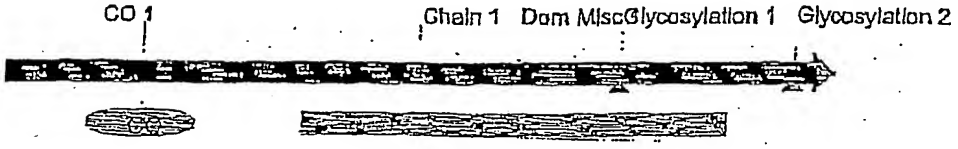
FIGURE 1: L Ficolin



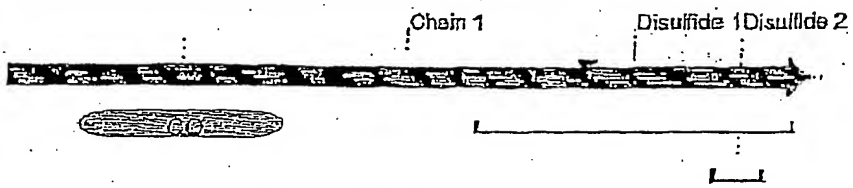
~~FCN2_HUMAN@2~~
~~313 aa~~

LQAAD TCPEVKMVGL EGSDKLTILR
GCPGLPGAPG DKGEAGTNGK RGERGPPGPP GKAGPPGPNG APSEPQPCLT
GPRTCKDLLD RGHFLSGWHT IYLPDCRPLT VLCDMDTDGG GWTVFQRRVD
GSVDFYRDWA TYKQGFGSRL GEFWLGNDNI HALTAQGTSE LRVDLVDFED
NYQFAKYRSF KVADEAEKYN LVLGAFVEGS AGDSLTFHNN QSFSTKDQDN
DLNTGNCAVM FQGAWWYKNC HVSNLNGRYL RGTHGSFANG INWKSGKGYN
YSYKVSEMKV RPA

~~Protein FCN2_HUMAN@2~~:

~~Ficolin-2 precursor (Collagen/fibrinogen domain-containing protein 2) (Ficolin-B) (Ficolin B) (Serum lectin P35) (HBP 35) (Ficolin) (L-Ficolin).~~

FIGURE 2: MBL



MBL-C HUMAN

GRDGTKGEKG ETVTCEDAQK TCPAVIACSS PGINGFPGKD
EPGQGLRGLQ GPPGKLGPPG NPGPSGSPGP KGQKGDPGKS
PDGDSSLAAS ERKALQTEMA RIKKWLTFSL GKQVGNKFFL TNGEIMTFEK
VKALCVKFQA SVATPRNAAE NGAIQNLIKE EAFLGITDEK TEGQFVDLTG
NRLTYTNWNE GEPNNAGSDE DCVLLLKNGQ WNDVPCSTSH LAVCEFPI

~~Protein MBL-C_HUMAN~~

~~MANNOSE-BINDING PROTEIN C PRECURSOR (MBP-C) (MBPT) (MANNAN-BINDING LECTIN) (MANNOSE-BINDING LECTIN)~~